Europäisches Patentamt
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(19)

(11) Publication number: **0 091 694 A1**

B6

(12) # EUROPEAN PATENT APPLICATION

(21) Application number: 83103562.1

(22) Date of filing: 13.04.83

(51) Int. Cl.³: C 07 C 103/60
C 07 C 103/66, C 07 C 102/04
A 61 K 31/16, A 61 K 31/215

(30) Priority: 13.04.82 JP 60310/82

(43) Date of publication of application: 19.10.83 Bulletin 83/42

(84) Designated Contracting States: AT BE CH DE FR GB IT LI NL SE

(71) Applicant: Eisai Co., Ltd.
6-10, Koishikawa 4-chome Bunkyo-ku
Tokyo 112(JP)

(72) Inventor: Yamatsu, Isao
3605-669, Ohaza Kashiwada Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: Suzuki, Takeshi
56-107, Sakaecho 1-chome Ushikumachi
Inashiki-gun Ibaragi(JP)

(72) Inventor: Abe, Shinya
40-2, Ohaza Shiroyama Kukisaki-mura
Inashiki-gun Ibaragi(JP)

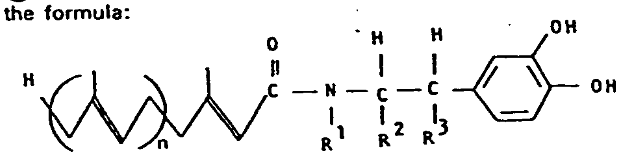
(72) Inventor: Kajiwara, Akiharu
29-4, Higashi Arai Yatabecho
Tsukuba-gun Ibaragi(JP)

(72) Inventor: Ota, Kiichiro
1-1, Benzaitenmachi
Wakayama-shi Wakayama(JP)

(74) Representative: Hansen, Bernd, Dr.rer.nat. et al,
Hoffmann, Eitle & Partner Patentanwälte
Arabellastrasse 4
D-8000 München 81(DE)

(54) **Polyprenylcarboxylic acid amides and process for preparing the same.**

(57) There is disclosed a polyprenylcarboxylic acid amide of the formula:



wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or an OH group and *n* represents an integer of 1 to 6.

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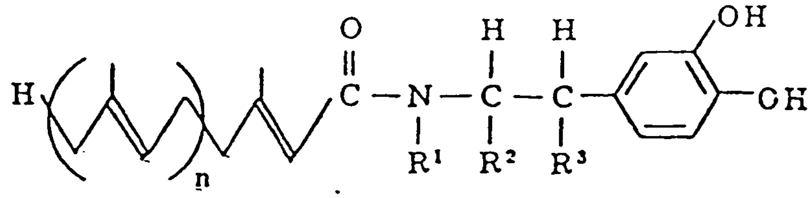
POLYPRENYLCARBOXYLIC ACID AMIDES AND PROCESS FOR PREPARING THE SAME

The present invention is related to a polyprenylcarboxylic acid amide, called also polyprenoic acid amide, which is useful as a medicine and a process for preparing the same. More in particular, the present invention relates to polyprenylcarboxylic acid amides of the general formula:



[I]

wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or an OH group and _n_ represents an integer of 1 to 6,

and a process for preparing them.

The lower alkyl groups in the definitions of R^1, R^2 and R^4 in the above general formula [I] are straight-chain or branched alkyl groups having 1 to 6 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, 1-methylpropyl, tert-butyl, n-pentyl, 1-ethylpropyl, isoamyl and n-hexyl group.

The polyprenylcarboxylic acids provided by the present invention are novel compounds not disclosed yet in literature. They have excellent physiological effects and are highly valuable as medicines.

The compounds of the present invention are derivatives of catecholamines such as dopamine, L-dopa, epinephrine, norepinephrine and isoproterenol. The

compounds exhibit the physiological effects of these catecholamines for a long time.

According to the inventors' experiments, they have a remarkable cyclic AMP-increasing effect, a long-lasting PTH (parathormone) secreting effect and a lasting β_2-agonistic effect.

Therefore, like norepinephrine and epinephrine, the compounds of the present invention are useful as adrenergic agents for the treatment or prevention of allergic diseases such as asthma, nasitis and hives and also as vasoconstrictor, hypotension remedy, cardiotonic drug; shock remedy and thrombopathy remedy. Further, they are also useful as remedies based on their cyclic AMP-increasing and lasting PTH secretion effects.

Typical examples of the compounds of the present invention are as follows, which by no means limit the invention:

N-(3,7-dimethyl-2,6-octadienoyl)dopamine,

N-(3,7,11-trimethyl-2,6,10-dodecatrienoyl)dopamine,

N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-dopamine,

N-(3,7,11,15,19-pentamethyl-2,6,10,14,18-eicosapentaenoyl)-dopamine,

N-(3,7,11,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosa-

hexaenoyl)dopamine.

N-(3,7,11,15,19,23,27-heptamethyl-2,6,10,14,18,22,26-octacosaheptaenoyl)dopamine,

methyl-N-(3,7-dimethyl-2,6-octadienoyl)-L-dopa,

methyl-N-(3,7,11-trimethyl-2,6,10-dodecatrienoyl)-L-dopa,

methyl-N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-L-dopa,

methyl-N-(3,7,11,15,19-pentamethyl-2,6,10,14,18-eicosapentaenoyl)-L-dopa,

methyl-N-(3,7,11,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaenoyl)-L-dopa,

methyl-N-(3,7,11,15,19,23,27-heptamethyl-2,6,10,18,22,26-octacosaheptaenoyl)-L-dopa,

N-(3,7-dimethyl-2,6-octadienoyl)-ℓ-epinephrine,

N-(3,7,11-trimethyl-2,6,10-dodecatrienoyl)-ℓ-epinephrine,

N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-ℓ-epinephrine,

N-(3,7,11,15,19-pentamethyl-2,6,10,14,18-eicosapentaenoyl)-ℓ-epinephrine,

N-(3,7,11,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaenoyl)-ℓ-epinephrine,

N-(3,7,11,15,19,23,27-heptamethyl-2,6,10,14,18,22,26-

octacosaheptaenoyl)-ℓ-epinephrine,

N-(3,7-dimethyl-2,6-octadienoyl)-ℓ-norepinephrine,

N-(3,7,11-trimethyl-2,6,10-dodecatrienoyl)-ℓ-norepinephrine,

N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-ℓ-norepinephrine,

N-(3,7,11,15,19-pentamethyl-2,6,10,14,18-eicosapentaenoyl)-ℓ-norepinephrine,

N-(3,7,11,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaenoyl)-ℓ-norepinephrine,

N-(3,7,11,15,19,23,27-heptamethyl-2,6,10,14,18,22,26-octacosaheptaenoyl)-ℓ-norepinephrine,

N-(3,7-dimethyl-2,6-octadienoyl)-dℓ-isoproterenol,

N-(3,7,11-trimethyl-2,6,10-undecatrienoyl)-dℓ-isoproterenol,

N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-dℓ-isoproterenol,

N-(3,7,11,15,19-pentamethyl-2,6,10,14,18-eicosapentaenoyl)-dℓ-isoproterenol,

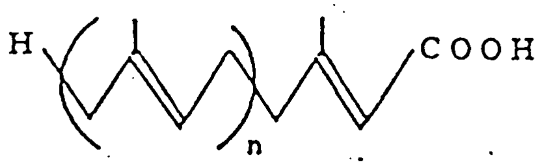
N-(3,7,11,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaenoyl)-dℓ-isoproterenol, and

N-(3,7,11,15,19,23,27-heptamethyl-2,6,10,14,18,22,26-octacosaheptaenoyl)-dℓ-isoproterenol.

Compounds [I] of the present invention can be prepared by various processes. An example of generally

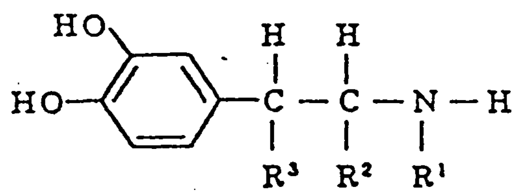
employed processes will be given below.

A polyprenylcarboxylic acid of the general formula [II]:



[II]

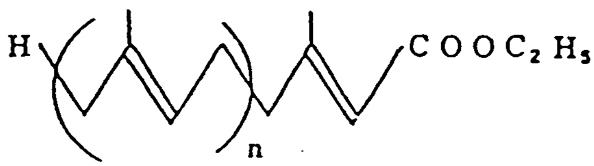
wherein $\underline{n}$ represents an integer of 1 to 6, or a reactive derivative thereof is reacted with an amino compound of the general formula [III]:



[III]

wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or a group of the formula -OH.

As the reactive derivatives of the polyprenylcarboxylic acids, there may be mentioned, for example, acid chlorides, acid anhydrides and acid azides. These reactive derivatives are not necessarily isolated



[V]

wherein n has the same meaning as above, and hydrolyzing the ethyl ester with, for example, a base such as KOH to form the polyprenylcarboxylic acid of the general formula [II].

Brief Description of Drawings:

Fig. 1 shows a PTH secretion effect of the compound of the present invention in bovine parathyroid cells.

The ordinates show the PTH concentration and the abscissae show the concentration of the compound of the present invention.

Fig. 2 shows changes in the PTH secretion effect of the compound of the present invention (10^{-5} M) with time in bovine parathyroid cells.

The ordinates show the PTH concentration and the abscissae show the time (min). The solid line shows changes in the PTH secretion effect with time observed when the compound of the present invention (10^{-5} M) was used and dotted line shows those observed when a control was used.

Fig. 3 shows a cyclic AMP-increasing effect of the compound of the present invention in bovine parathyroid cells. The ordinates show the amount of cyclic AMP and abscissae show the concentration of the compound of the present invention.

Fig. 4 shows the effect of epinephrine on PTH in the blood plasma.

The ordinates show the concentration of PTH and the abscissae show the amount of epinephrine.

Fig. 5 shows PTH increase in the blood plasma observed 5 min after the administration of the compound of the present invention to rats.

The ordinates show the concentration of PTH and the abscissae show the amount of the compound of the present invention.

Fig. 6 shows PTH increase in the blood plasma observed 1 min after the administration of the compound of the present invention to rats.

The ordinates show the concentration of PTH and the abscissae show the amount of the compound of the present invention.

Fig. 7 shows cyclic AMP increase in the blood plasma observed 5 min after the administration of the compound of the present invention to rats.

The ordinates show the concentration of cyclic

AMP in the blood plasma and the abscissae show the amount of the compound of the present invention.

Fig. 8 shows cyclic AMP increase in the blood plasma observed 1 min after the administration of the compound of the present invention to rats.

The ordinates show the concentration of cyclic AMP in the blood plasma and the abscissae show the amount of the compound of the present invention.

Excellent physiological effects of typical compounds of the present invention will be illustrated below.

Experiments:

PTH (parathormone) secretion and cyclic AMP-increasing effects:

(1) Method of experiments:

A test compound was dissolved in lecithin liposome and 150 μℓ in total of the sample was injected into femoral veins of Wistar rats weighing 150 g after fasting for 24 h. 1 and 5 min after the injection, the blood was taken from the abdominal main artery. 50 μℓ of 500 mM EDTA (pH 7.45) was charged in a test tube and then 3 mℓ of the blood from the abdominal main artery was added thereto. After stirring, the mixture was centrifuged in a refrigerated centrifuge at 2,000 rpm for 10 min. The blood plasma was taken.

PTH and cyclic AMP contained in the blood plasma were determined. PTH was determined by means of radio-immunoassay.

As the test compound, N-(3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl)-ℓ-epinephrine was used.

(2) Results:

The results are shown in Figs. 1 to 8.

Fig. 1 shows the results of the examination of PTH secretion in bovine parathyroid cells carried out by preparing a concentration gradient of the test compound with a solubilizer. The abscissae show the concentration of the test compound and the ordinates show the amount of PTH.

It is apparent from Fig. 1 that PTH is secreted in proportion to the amount of the test compound in the concentration range of 10^{-7} to 10^{-3} M.

Fig. 2 shows the results of the examination of PTH secretion with time carried out by using parathyroid cells with a test compound concentration of 10^{-5} M. The abscissae show the time (min) and the ordinates show the amount of PTH.

Fig. 3 shows the results of the examination of release of cyclic AMP in the culture liquid of parathyroid cells carried out by preparing a concentration gradient of the test compound. The abscissae show the

concentration of the test compound and the ordinates show the amount of cyclic AMP.

It is apparent from Fig. 3 that cyclic AMP was released from the parathyroid cells in proportion to the amount of the test compound in a concentration range of up to 10^{-4} M.

Fig. 4 shows the results of the examination of the amount of PTH in blood plasma obtained carried out by injecting 1.0 to 5.0 mg/kg-body weight of Wistar male rats of epinephrine into femoral veins of the rats. The abscissae show the concentration of epinephrine and the ordinates show the amount of PTH.

It is apparent from Fig. 4 that the maximum PTH secretion was obtained with 2.5 mg/kg-body weight of epinephrine. With a higher concentration of epinephrine, the secretion was rather inhibited.

Fig. 5 shows the results obtained by injecting 0.01, 0.1, 1 and 5 mg/kg-body weight of the test compound into Wistar male rats weighing 150 g and examining PTH in the blood plasma after 5 min. The abscissae show the concentration of the test compound and the ordinates show the amount of PTH.

It is apparent from Fig. 5 that PTH in the blood plasma was increased in proportion to the amount of the test compound in the range of 0.1 to 5 mg/kg.

Fig. 6 shows the results obtained by administering 5, 10 and 53 mg/kg of the test compound by intravenous injection to Wistar male rats weighing 150 g and examining blood plasma PTH after one min. The abscissae show the concentration of the test compound and the ordinates show the amount of PTH.

It is apparent from Fig. 6 that the maximum secretion was observed when 5 or 10 mg/kg-body weight of the test compound was injected into the rats.

Fig. 7 shows the results of the examination of influences of 0.01, 0.1, 1 and 5 mg/kg-body weight of the test compound on cyclic AMP in the blood plasma of Wistar male rats weighing 150 g 5 min after the injection. The abscissae show the concentration of the test compound and the ordinates show the amount of cyclic AMP.

It is apparent from Fig. 7 that cyclic AMP in the blood plasma was increased in proportion to the concentration of the test compound in the range of 0.01 to 5 mg/kg.

Fig. 8 shows the results of examination obtained by injecting 5, 10 and 53 mg/kg-body weight of the test compound into Wistar male rats weighing 150 g and examining influences thereof on cyclic AMP in the blood plasma one min after the injection.

It is apparent from Fig. 8 that the maximum cyclic AMP releasing effect in blood plasma was obtained with 10 mg/kg-body weight of the test compound.

(3) Conclusion:

It is apparent from the above experimental results that effects of the test compound on PTH secretion and cyclic AMP release obtained by using bovine parathyroid cells were in proportion to the amount of the compound and that the PTH secretion lasted for a long time. This fact indicates that the compound of the present invention has a continuous PTH-secreting effect, while epinephrine has a pulse-like PTH secretion effect.

In the experiments using rats, the test compound exhibited a blood plasma cyclic AMP-increasing effect.

It is apparent from the above experiments that the compound of the present invention has remarkable cyclic AMP-increasing and continuous PTH secretion effects. The compound is usable as an adrenergic agent for the treatment or prevention of allergic diseases such as asthma, nasitis and hives and also as local vasoconstrictor, hypotension remedy, cardiotonic drug, shock remedy and thrombopathy remedy. The compound is thus quite valuable.

The compounds of the present invention are used in

the form of tablets, granules, powders, capsules, injections and suppositories prepared by ordinary methods employed in the art.

In preparing an oral solid preparation, an excipient and, if necessary, a binder, disintegrator, lubricant, colorant and corrigent are added to the basis and then the mixture is shaped into tablets, coated tablets, granules, powders or capsules by an ordinary method.

As the excipients, there may be used, for example, lactose, corn starch, white sugar, sorbitol, crystalline cellulose and silicon dioxide. As the binders, there may be used, for example, polyvinyl alcohol, polyvinyl ether, ethylcellulose, methylcellulose, acacia, tragacanth, gelatin, shellac, hydroxypropylcellulose, hydroxypropylstarch and polyvinylpyrrolidone. As the disintegrators, there may be used, for example, starch, agar, gelatin powder, crystalline cellulose, calcium carbonate, sodium hydrogencarbonate, calcium citrate, dextrin and pectin. As the lubricants, there may be used, for example, magnesium stearate, talc, polyethylene glycol, silica and hardened vegetable oils. As the colorants, there may be used those allowed as colorants for medicines. As the corrigents, there may be used, for example, cocoa powder, menthol,

aromatic powder, peppermint oil, borneol and cinnamon powder. As a matter of course, these tablets and granules may be coated suitably with sugar, gelatin or the like.

In the preparation of an injection, if necessary, a pH regulator, buffer agent, stabilizer, preservative, solubilizer and suspending agent are added to the basis and subcutaneous injection, intramuscular injection or intravenous injection is prepared from the mixture.

The following examples will further illustrate the present invention, which by no means limit the invention.

Example 1

N-(E- and Z-3,7-dimethyl-2,6-octadienoyl)dopamine:

17 g of E- and Z-3,7-dimethyl-2,6-octadienoic acid was dissolved in 100 mℓ of anhydrous benzene. 20 mℓ of thionyl chloride was added to the solution and the mixture was heated under reflux. After 30 min, benzene and excessive thionyl chloride were distilled off under reduced pressure.

Then, 19 g of dopamine hydrochloride was dissolved in 100 mℓ of dimethylformaide (DMF) and 15 mℓ of triethylamine was added to the solution. The acid chloride obtained as above was added dropwise to this

solution under stirring and cooling with ice. After carrying out the reaction for 1 h, the reaction mixture was added to ice-water and extracted with 200 mℓ of ether. After washing with water, the extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrated product was crystallized from benzene to obtain 20 g of the intended compound, i.e. N-(E- and Z-3,7-dimethyl-2,6-octadienoyl)dopamine as white needle-like crystals.

M.p.: 103.5-104.5°C

Elementary analysis as $C_{18}H_{25}NO_3$:

	C	H	N
Calculated (%)	71.25	8.31	4.62
Found (%)	71.24	8.32	4.64

NMR ($CDCl_3$, δ)

6.8-7.1 (broad, 2H), 6.4-6.9 (m, 3H)
5.80 (m, 1H), 5.54 (m, 1H)
5.10 (m, 1H), 3.42 (m, 2H)
2.65 (m, 2H), 1.80-2.30 (m, 4H)
1.80, 1.68, 1.60 (s, 9H)

Example 2

N-[(E,E,E)- and (Z,E,E.)-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl]dopamine:

7.1 g of (E,E,E)- and (Z,E,E)-3,7,11,15-tetramethyl-

2,6,10,14-hexadecatetraenoic acid was dissolved in 200 mℓ of anhydrous ether. 10 mℓ of triethylamine was added to the solution. 3 g of ethyl chlorocarbonate was added dropwise to the mixture under stirring and cooling with ice. After carrying out the reaction for 1 hour, the reaction mixture was poured in iced water. The organic layer was washed with dilute hydrochloric acid and then with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. 5.7 g of dopamine hydrochloride was dissolved in 50 mℓ of dimethylformamide. 10 mℓ of triethylamine was added to the solution. The acid anhydride obtained as above was added dropwise to this solution at room temperature. After carrying out the reaction for 1 h, the reaction mixture was poured in ice-water and extracted with 200 mℓ of ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrate was purified according to silica gel column chromatography to obtain 5.2 g of the intended compound, i.e., N-[(E,E,E)- and (Z,E,E)-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl]dopamine, as colorless oily product.

Elementary analysis as $C_{28}H_{41}NO_3$:

	C	H	N
Calculated (%)	76.49	9.40	3.19
Found (%)	76.50	9.40	3.18

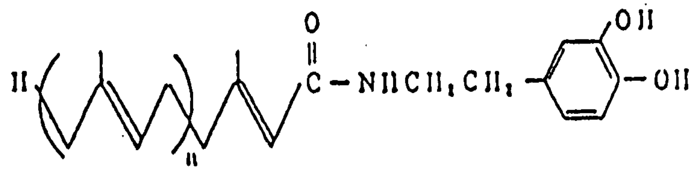
NMR ($CDCl_3$, δ)

6.8-7.2 (broad, 2H), 6.4-6.8 (m, 3H)
5.80 (m, 1H), 5.54 (m, 1H)
5.10 (m, 3H), 3.42 (m, 2H)
2.65 (m, 2H), 1.80-2.30 (m, 12H)
1.80, 1.68, 1.60 (s, 15H)

Examples 3 to 6

Compounds shown in Table 1 were synthesized in the same manner as in Example 1 or 2.

<u>Table 1</u>



Example	n	Molecular formula	Elementary analysis	C (%)	H (%)	N (%)	NMR ($CDCl_3$, δ)
3	2	$C_{23}H_{33}NO_3$	Calcd.	74.36	8.95	3.77	6.8～7.1 (broad, 2H), 6.4～6.9 (m, 3H), 5.80 (m, 1H), 5.54 (m, 1H), 5.10 (m, 2H) 3.42 (m, 2H), 2.65 (m, 2H). 1.80～2.30 (m, 8H), 1.80, 1.68, 1.60 (s, 12H)
			Found	74.33	8.94	3.79	
4	4	$C_{33}H_{49}NO_3$	Calcd.	78.06	9.73	2.76	6.8～7.2 (broad, 2H), 6.4～6.8 (m, 3H), 5.80 (m, 1H), 5.54 (m, 1H), 5.10 (m, 4H), 3.42 (m, 2H), 2.65 (m, 2H), 1.80～2.30 (m, 16H), 1.80, 1.68, 1.60 (s, 18H)
			Found	78.05	9.74	2.75	
5	5	$C_{38}H_{58}NO_3$	Calcd.	79.25	9.98	2.43	6.8～7.2 (broad, 2H), 6.4～6.8 (m, 3H), 5.80 (m, 1H), 5.54 (m, 1H), 5.10 (m, 5H), 3.42 (m, 2H), 2.65 (m, 2H), 1.80～2.30 (m, 20H), 1.80, 1.68, 1.60 (s, 21H)
			Found	79.25	9.98	2.42	
6	6	$C_{43}H_{65}NO_3$	Calcd.	80.20	10.17	2.18	6.8～7.2 (broad, 2H), 6.4～6.8 (m, 3H), 5.80 (m, 1H), 5.54 (m, 1H), 5.10 (m, 6H), 3.42 (m, 2H), 2.65 (m, 2H), 1.80～2.30 (m, 24H), 1.80, 1.68, 1.60 (s, 24H)
			Found	80.20	10.16	2.17	

Example 7

Methyl-N-[(E,E,E)- and (Z,E,E)-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl]-L-dopa:

6.1 g of (E,E,E)- and (Z,E,E)-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoic acid was dissolved in 100 mℓ of anhydrous benzene. 10 mℓ of thionyl chloride was added to the solution and the mixture was heated under reflux. After 30 min, benzene and excessive thionyl chloride were distilled off under reduced pressure. 5 g of methyl-L-dopa hydrochloride was dissolved in 100 mℓ of dimethylformamide and 10 mℓ of triethylamine was added to the solution. The acid chloride obtained as above was added dropwise to this solution under stirring and cooling with ice. After carrying out the reaction for 1 h, the reaction mixture was poured into ice-water and extracted with 200 mℓ of ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The resulting concentrate was purified according to silica gel chromatography to obtain 4.6 g of the intended compound, i.e., methyl-N-[(E,E,E)- and (Z,E,E)-3,7,11,15-tetramethyl-2,6,10,14-hexadecatetraenoyl]-L-dopa.

Elementary analysis as $C_{35}H_{51}NO_5$:

	C	H	N
Calculated (%)	74.30	9.09	2.48
Found (%)	74.29	9.10	2.48

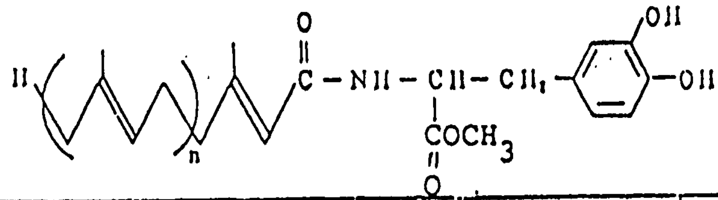
NMR ($CDCl_3$, δ):

6.9-7.2 (broad, 2H), 6.3-6.8 (m, 3H)
6.02 (d, 1H, J=8Hz), 5.58 (m, 1H)
5.10 (m, 4H), 4.85 (m, 1H), 3.72 (s, 3H)
3.00 (d, 2H, J=6Hz), 1.80-2.30 (m, 16H)
1.79, 1.65, 1.60 (s, 18H)

Examples 8 to 12

Compounds shown in Table 2 were synthesized in the same manner as in Example 7.

Table 2



Example	n	Molecular formula	Elementary analysis				NMR ($CDCl_3$, δ)
				C(%)	H(%)	N(%)	
8	1	$C_{20}H_{27}NO_5$	Calcd.	66.46	7.53	3.88	6.9~7.2 (broad, 2H), 6.3~6.8 (m, 3H), 6.00 (d, 1H, J=8Hz), 5.56 (m, 1H), 5.10 (m, 1H), 4.84 (m, 1H), 3.70 (s, 3H), 2.98 (d, 2H, J=6Hz), 1.80~2.30 (m, 4H), 1.79, 1.65, 1.60 (s, 9H)
			Found	66.45	7.53	3.90	
				C(%)	H(%)	N(%)	
9	2	$C_{25}H_{35}NO_5$	Calcd.	69.90	8.21	3.26	6.9~7.2 (broad, 2H), 6.3~6.8 (m, 3H), 6.00 (d, 1H, J=8Hz), 5.56 (m, 1H), 5.10 (m, 2H), 4.84 (m, 1H), 3.70 (s, 3H), 3.00 (d, 2H, J=6Hz), 1.80~2.30 (m, 8H), 1.79, 1.65, 1.60 (s, 12H)
			Found	69.90	8.20	3.24	
				C(%)	H(%)	N(%)	
10	3	$C_{30}H_{43}NO_5$	Calcd.	72.40	8.71	2.81	6.9~7.2 (broad, 2H), 6.3~6.8 (m, 3H), 6.02 (d, 1H, J=8Hz), 5.56 (m, 1H), 5.10 (m, 3H), 4.85 (m, 1H), 3.70 (s, 3H), 3.00 (d, 2H, J=6Hz), 1.80~2.30 (m, 12H), 1.79, 1.65, 1.60 (s, 15H)
			Found	72.38	8.71	2.80	
				C(%)	H(%)	N(%)	
11	5	$C_{40}H_{59}NO_5$	Calcd.	75.79	9.38	2.21	6.9~7.2 (broad, 2H), 6.3~6.8 (m, 3H), 6.02 (d, 1H, J=8Hz), 5.59 (m, 1H), 5.10 (m, 5H), 4.85 (m, 1H), 3.72 (s, 3H), 3.00 (d, 2H, J=6Hz), 1.80~2.30 (m, 20H), 1.79, 1.65, 1.60 (s, 21H)
			Found	75.80	9.38	2.19	
				C(%)	H(%)	N(%)	
12	6	$C_{45}H_{67}NO_5$	Calcd.	76.99	9.62	2.00	6.9~7.2 (broad, 2H), 6.3~6.8 (m, 3H), 6.02 (d, 1H, J=8Hz), 5.58 (m, 1H), 5.10 (m, 6H), 4.85 (m, 1H), 3.72 (s, 3H), 3.00 (d, 2H, J=6Hz), 1.80~2.30 (m, 24H), 1.79, 1.65, 1.60 (s, 24H)
			Found	76.98	9.63	2.01	

Example 13

N-[(E,E)- and (E,Z)-3,7,11-trimethyl-2,6,10-undecatrienoyl]-ℓ-epinephrine:

7.4 g of (E,E)- and (E,Z)-3,7,11-trimethyl-2,6,10-undecatrienoic acid was dissolved in 200 mℓ of anhydrous ether. 10 mℓ of triethylamine was added to the solution and then 5 g of ethyl chlorocarbonate was added dropwise thereto under stirring under cooling. After carrying out the reaction for 1 h, the reaction mixture was poured into iced water. An organic layer was washed with dilute hydrochloric acid and then with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure.

Ten grams of epinephrine bitartrate was suspended in HMPA and 10 mℓ of water and 18 mℓ of triethylamine were added to the suspension. The acid anhydride obtained as above was added dropwise to this mixture at room temperature. After carrying out the reaction for 1 h, the reaction mixture was poured into ice-water and then extracted with 200 mℓ of ether. The extract was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The concentrate was purified according to silica gel column chromatography to obtain 5.5 g of the intended compound, i.e., N-[(E,E)- and (E,Z)-3,7,11-trimethyl-

2,6,10-undecatrienoyl]-ℓ-epinephrine.

Elementary analysis as $C_{24}H_{35}NO_4$:

	C	H	N
Calculated (%)	71.79	8.79	3.49
Found (%)	71.80	8.79	3.50

NMR ($CDC\ell_3$, δ):

6.5-6.9 (broad, 2H), 6.7-7.0 (m, 3H), 5.74, 5.50 (m, 1H), 5.10 (m, 2H), 4.93 (m, 1H), 3.2-3.9 (m, 2H), 2.92 (s, 3H), 1.8-2.3 (m, 9H), 1.76, 1.69, 1.59 (s, 12H)

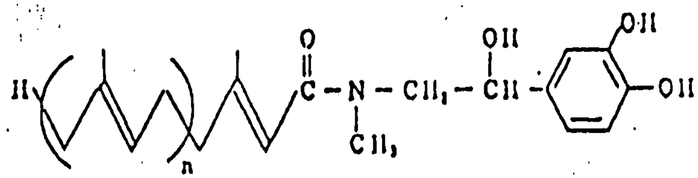
Examples 14 to 18

Compounds shown in Table 3 were obtained using corresponding carboxylic acids in the same manner as in Example 13.

Examples 19 to 30

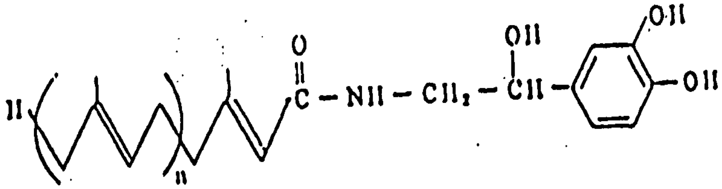
Compounds shown in Tables 4 and 5 were obtained using ℓ-norepinephrine tartrate and dℓ-isoproterenol hydrochloride in the same manner as in Example 13.

Table 3



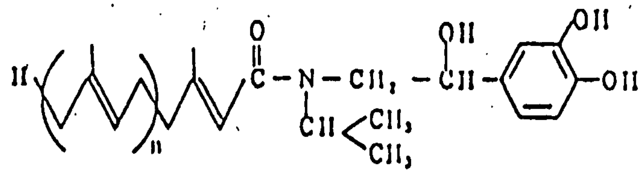
Example	n	Molecular formula	Elementary analysis				NMR ($CDCl_3$, δ)
				C(%)	H(%)	N(%)	
14	1	$C_{19}H_{27}NO_4$	Calcd.	68.44	8.16	4.20	6.5~6.9 (broad, 2H), 6.7~7.0 (m, 3H), 5.74~5.50 (m, 1H), 5.10 (m, 1H), 4.92 (m, 1H), 3.2~3.9 (m, 2H), 2.92 (s, 3H), 1.80~2.30 (m, 5H), 1.76, 1.68, 1.58 (s, 9H)
			Found	68.44	8.16	4.22	
				C(%)	H(%)	N(%)	
15	3	$C_{29}H_{43}NO_4$	Calcd.	74.16	9.23	2.98	6.5~6.9 (broad, 2H), 6.7~7.0 (m, 3H), 5.74, 5.50 (m, 1H), 5.10 (m, 3H), 4.93 (m, 1H), 3.2~3.9 (m, 2H), 2.92 (s, 3H), 1.8~2.3 (m, 13H), 1.76, 1.69, 1.60 (s, 15H)
			Found	74.15	9.24	2.96	
				C(%)	H(%)	N(%)	
16	4	$C_{34}H_{51}NO_4$	Calcd.	75.93	9.56	2.60	6.5~6.9 (broad, 2H), 6.7~7.0 (m, 3H), 5.74, 5.50 (m, 1H), 5.10 (m, 4H), 4.93 (m, 1H), 3.2~3.9 (m, 2H), 2.92 (s, 3H), 1.8~2.3 (m, 17H), 1.76, 1.68, 1.58 (s, 18H)
			Found	75.93	9.56	2.59	
				C(%)	H(%)	N(%)	
17	5	$C_{39}H_{59}NO_4$	Calcd.	77.31	8.21	2.31	6.5~6.9 (broad, 2H), 6.7~7.0 (m, 3H), 5.74, 5.50 (m, 1H), 5.10 (m, 5H), 4.92 (m, 1H), 3.2~3.9 (m, 2H), 2.91 (s, 3H), 1.8~2.3 (m, 21H), 1.77, 1.69, 1.60 (s, 21H)
			Found	77.32	9.82	2.29	
				C(%)	H(%)	N(%)	
18	6	$C_{44}H_{67}NO_4$	Calcd.	78.41	10.02	2.08	6.5~6.9 (broad, 2H), 6.7~7.0 (m, 3H), 5.74, 5.50 (m, 1H), 5.10 (m, 6H), 4.92 (m, 1H), 3.2~3.9 (m, 2H), 2.90 (s, 3H), 1.8~2.3 (m, 25H), 1.78, 1.69, 1.60 (s, 24H)
			Found	78.40	10.21	2.09	

Table 4



Example	n	Molecular formula	Elementary analysis	C(%)	H(%)	N(%)	NMR ($CDCl_3$, δ)
19	1	$C_{18}H_{25}NO_4$	Calcd.	67.69	7.89	4.39	6.7~7.8 (broad, 2H), 6.4~6.8 (m, 3H), 6.42 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 1H), 4.52 (m, 1H), 3.36 (m, 2H), 1.8~2.3 (m, 5H), 1.78, 1.68, 1.60 (s, 9H)
			Found	67.68	7.88	4.41	
20	2	$C_{23}H_{33}NO_4$	Calcd.	71.29	8.58	3.61	6.7~7.2 (broad, 2H), 6.4~6.8 (m, 3H), 6.40 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 2H), 4.53 (m, 1H), 3.35 (m, 2H), 1.8~2.3 (m, 9H), 1.78, 1.68, 1.60 (s, 12H)
			Found	71.30	8.58	3.61	
21	3	$C_{28}H_{41}NO_4$	Calcd.	73.81	9.07	3.07	6.8~7.5 (broad, 2H), 6.4~6.8 (m, 3H), 6.41 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 3H), 4.53 (m, 1H), 3.36 (m, 2H), 1.8~2.3 (m, 13H), 1.78, 1.68, 1.60 (s, 15H)
			Found	73.80	9.07	3.09	
22	4	$C_{33}H_{49}NO_4$	Calcd.	75.67	9.43	2.67	6.8~7.5 (broad, 2H), 6.4~6.8 (m, 3H), 6.40 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 4H), 4.52 (m, 1H), 3.37 (m, 2H), 1.8~2.3 (m, 17H), 1.78, 1.68, 1.60 (s, 18H)
			Found	75.67	9.42	2.69	
23	5	$C_{38}H_{57}NO_4$	Calcd.	77.11	9.71	2.37	6.8~7.5 (broad, 2H), 6.4~6.8 (m, 3H), 6.40 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 5H), 4.52 (m, 1H), 3.37 (m, 2H), 1.8~2.3 (m, 21H), 1.78, 1.68, 1.60 (s, 21H)
			Found	77.10	9.72	2.37	
24	6	$C_{43}H_{65}NO_4$	Calcd.	78.25	9.93	2.12	6.8~7.5 (broad, 2H), 6.4~6.8 (m, 3H), 6.40 (broad, 1H), 5.54 (m, 1H), 5.10 (m, 6H), 4.52 (m, 1H), 3.37 (m, 2H), 1.8~2.3 (m, 25H), 1.78, 1.68, 1.60 (s, 24H)
			Found	78.23	9.93	2.12	

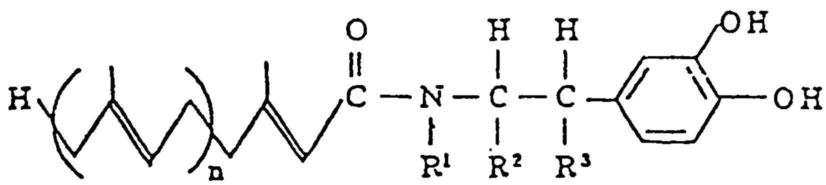
Table 5



Example	n	Molecular formula	Elementary analysis	C(%)	H(%)	N(%)	N M R ($CDCl_3$, δ)
25	1	$C_{21}H_{31}NO_4$	Calcd.	69.77	8.65	3.88	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H), 5.10 (m, 1H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 5H), 1.78, 1.68, 1.59 (s, 9H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	69.78	8.66	3.85	
26	2	$C_{26}H_{39}NO_4$	Calcd.	72.69	9.15	3.26	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H), 5.10 (m, 2H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 9H), 1.78, 1.68, 1.60 (s, 12H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	72.68	9.15	3.24	
27	3	$C_{31}H_{47}NO_4$	Calcd.	74.81	9.52	2.81	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H), 5.10 (m, 3H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 13H), 1.78, 1.68, 1.60 (s, 15H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	74.81	9.52	2.83	
28	4	$C_{36}H_{55}NO_4$	Calcd.	76.41	9.80	2.48	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H), 5.10 (m, 4H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 17H), 1.78, 1.68, 1.60 (s, 18H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	76.42	9.80	2.48	
29	5	$C_{41}H_{63}NO_4$	Calcd.	77.68	10.02	2.21	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H), 5.10 (m, 5H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 21H), 1.78, 1.68, 1.60 (s, 21H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	77.69	10.03	2.19	
30	6	$C_{46}H_{71}NO_4$	Calcd.	78.69	10.19	2.00	6.2~7.0 (broad, 2H), 6.6~7.1 (m, 3H), 5.92 (m, 1H) 5.10 (m, 6H), 4.76 (m, 1H), 2.95~4.36 (m, 3H), 1.8~2.4 (m, 25H), 1.78, 1.68, 1.60 (s, 24H), 1.22, 1.04 (d, 6H, J=7Hz)
			Found	78.70	10.19	2.01	

CLAIMS

(1) Polyprenylcarboxylic acid amides of the general formula:



wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or an OH group and n represents an integer of 1 to 6.

(2) Polyprenylcarboxylic acid amides according to Claim 1 wherein R^1, R^2 and R^3 represent a hydrogen atom and n represents an integer of 1 to 6.

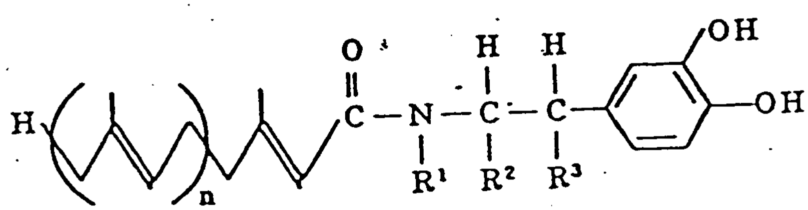
(3) Polyprenylcarboxylic acid amides according to Claim 1 wherein R^1 represents a hydrogen atom, R^2 represents $-COOCH_3$, R^3 represents a hydrogen atom and n represents an integer of 1 to 6.

(4) Polyprenylcarboxylic acid amides according to Claim 1 wherein R^1 represents a methyl group, R^2 represents a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

(5) Polyprenylcarboxylic acid amides according to Claim 1 wherein R^1 and R^2 represent each a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

(6) Polyprenylcarboxylic acid amides according to Claim 1 wherein R^1 represents an isopropyl group, R^2 represents a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

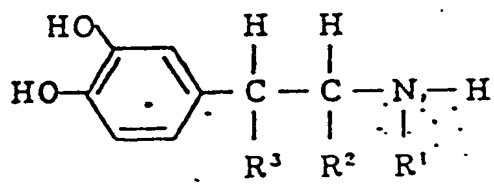
(7) A process for preparing polyprenylcarboxylic acid amides of the general formula:



wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or an OH group and n represents an integer of 1 to 6,

characterized by reacting a polyprenylcarboxylic acid of the general formula:

wherein n has the same meaning as above, or a reactive derivative thereof with an amino compound of the general formula:

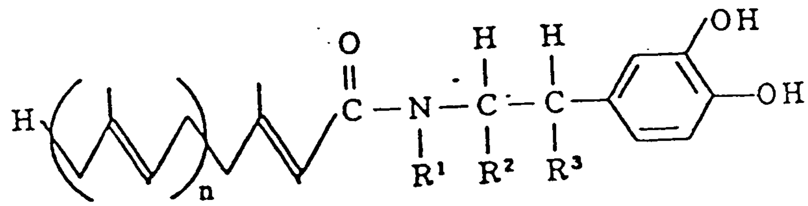


wherein R^1, R^2 and R^3 have the same meaning as above.

(8) Pharmaceutical composition comprising a compound according to claims 1 to 6 in a pharmaceutically effective amount together with a suitable carrier or diluent.

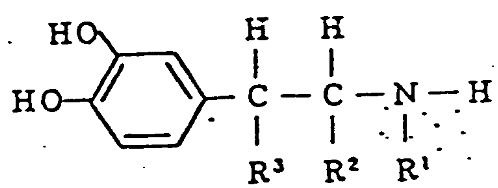
Claims

1. A process for preparing polyprenylcarboxylic acid amides of the general formula



wherein R^1 represents a hydrogen atom or a lower alkyl group, R^2 represents a hydrogen atom or a group of the formula: $-COOR^4$ in which R^4 represents a lower alkyl group, R^3 represents a hydrogen atom or an OH group and <u>n</u> represents an integer of 1 to 6, characterized by reacting a polyprenylcarboxylic acid of the general formula:

wherein <u>n</u> has the same meaning as above, or a reactive derivative thereof with an amino compound of the general formula:



wherein R^1, R^2 and R^3 have the same meaning as above.

2. A process for preparing polyprenylcarboxylic acid amides according to claim 1, wherein R^1, R^2 and R^3 represent a hydrogen atom and n represents an integer of 1 to 6.

3. A process for preparing polyprenylcarboxylic acid amides according to claim 1, wherein R^1 represents a hydrogen atom, R^2 represents $-COOCH_3$, R^3 represents a hydrogen atom and n represents an integer of 1 to 6.

4. A process for preparing polyprenylcarboxylic acid amides according to claim 1, wherein R^1 represents a methyl group, R^2 represents a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

5. A process for preparing polyprenylcarboxylic acid amides according to claim 1, wherein R^1 and R^2 represent each a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

6. A process for preparing polyprenylcarboxylic acid amides according to claim 1, wherein R^1 represents an isopropyl group, R^2 represents a hydrogen atom, R^3 represents a hydroxyl group and n represents an integer of 1 to 6.

FIG.1

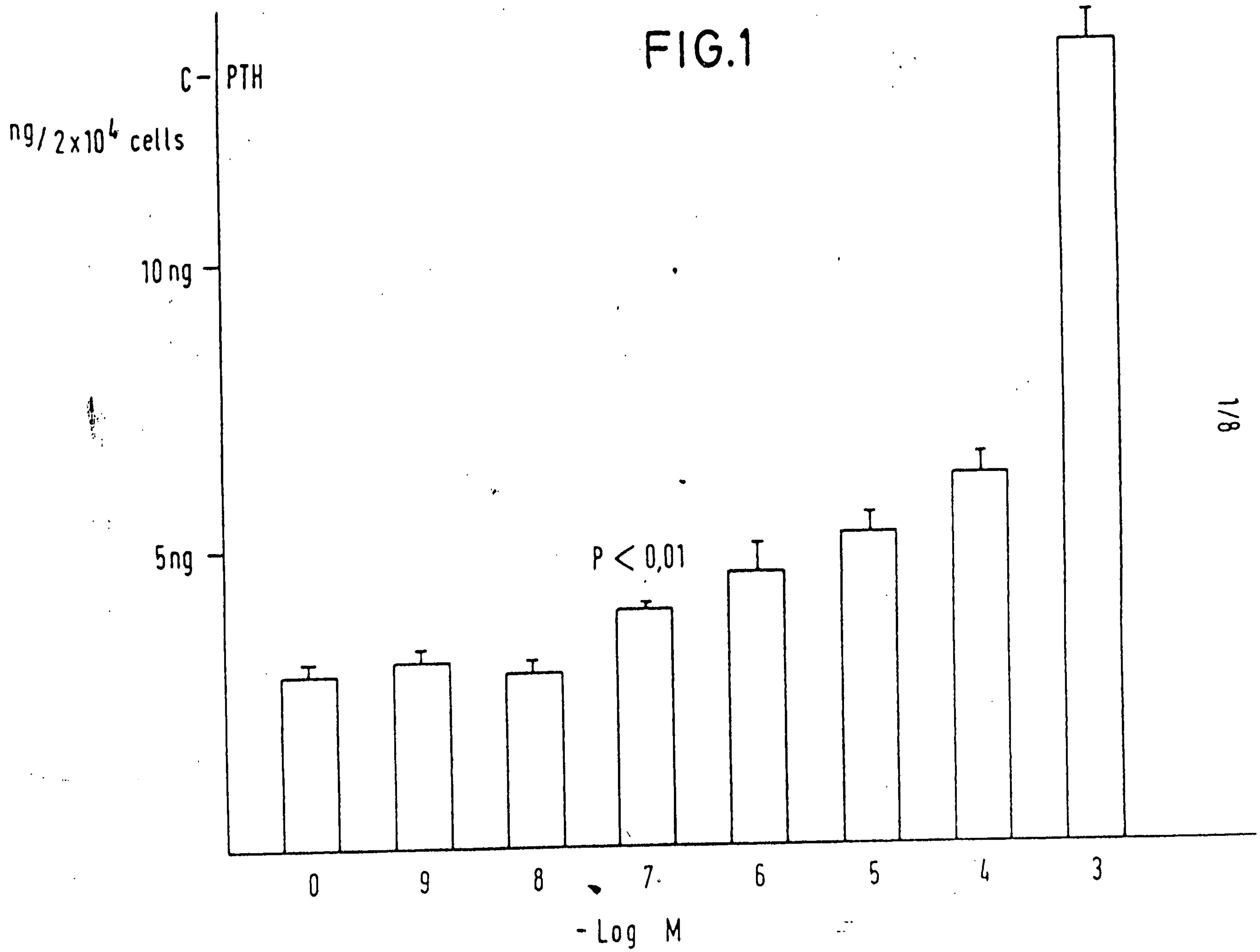


FIG.2

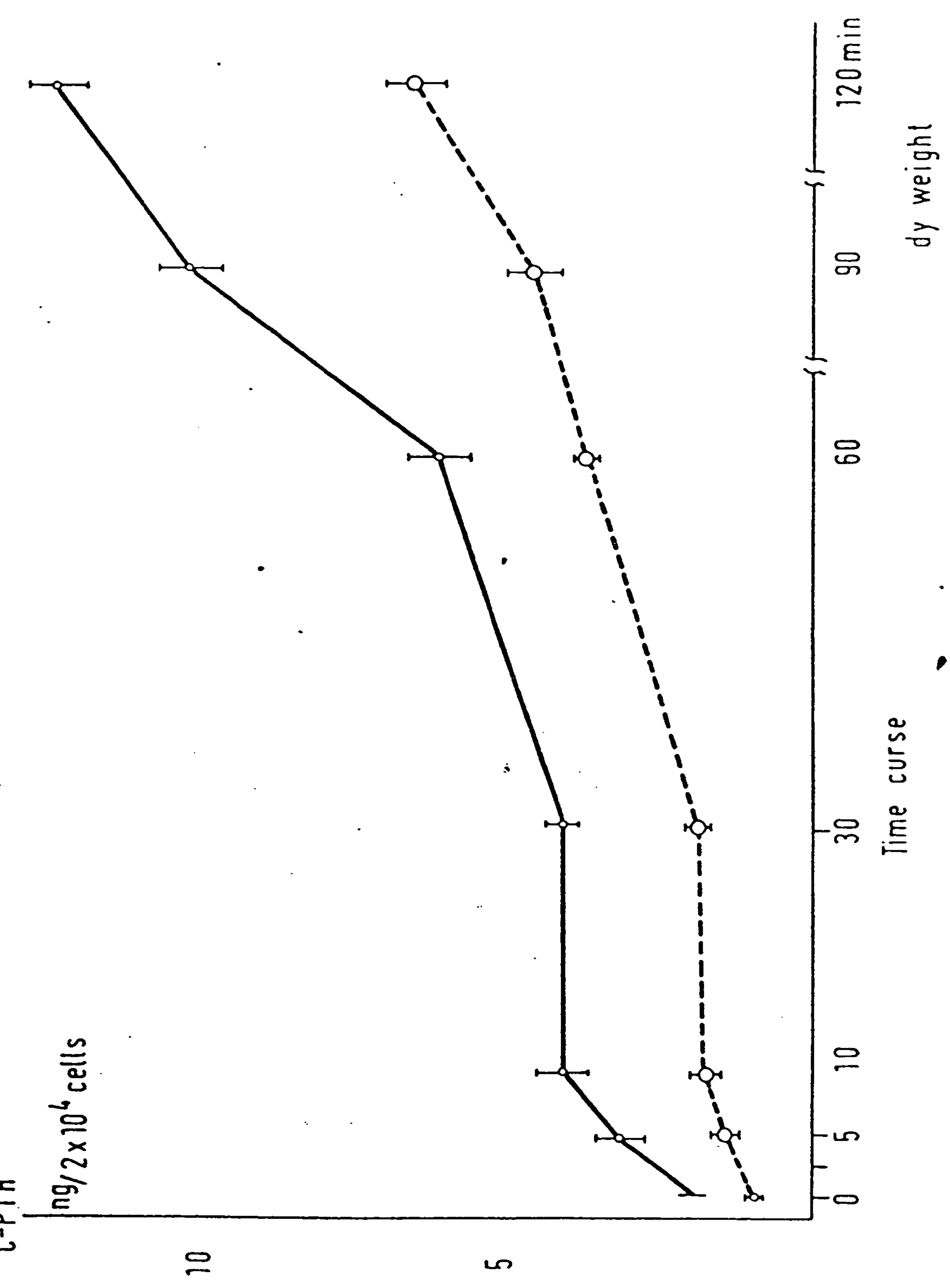

C-PTH
ng/2x10⁴cells
10
5
0
5
10
30
60
90
120 min
Time curse
dy weight

FIG.3

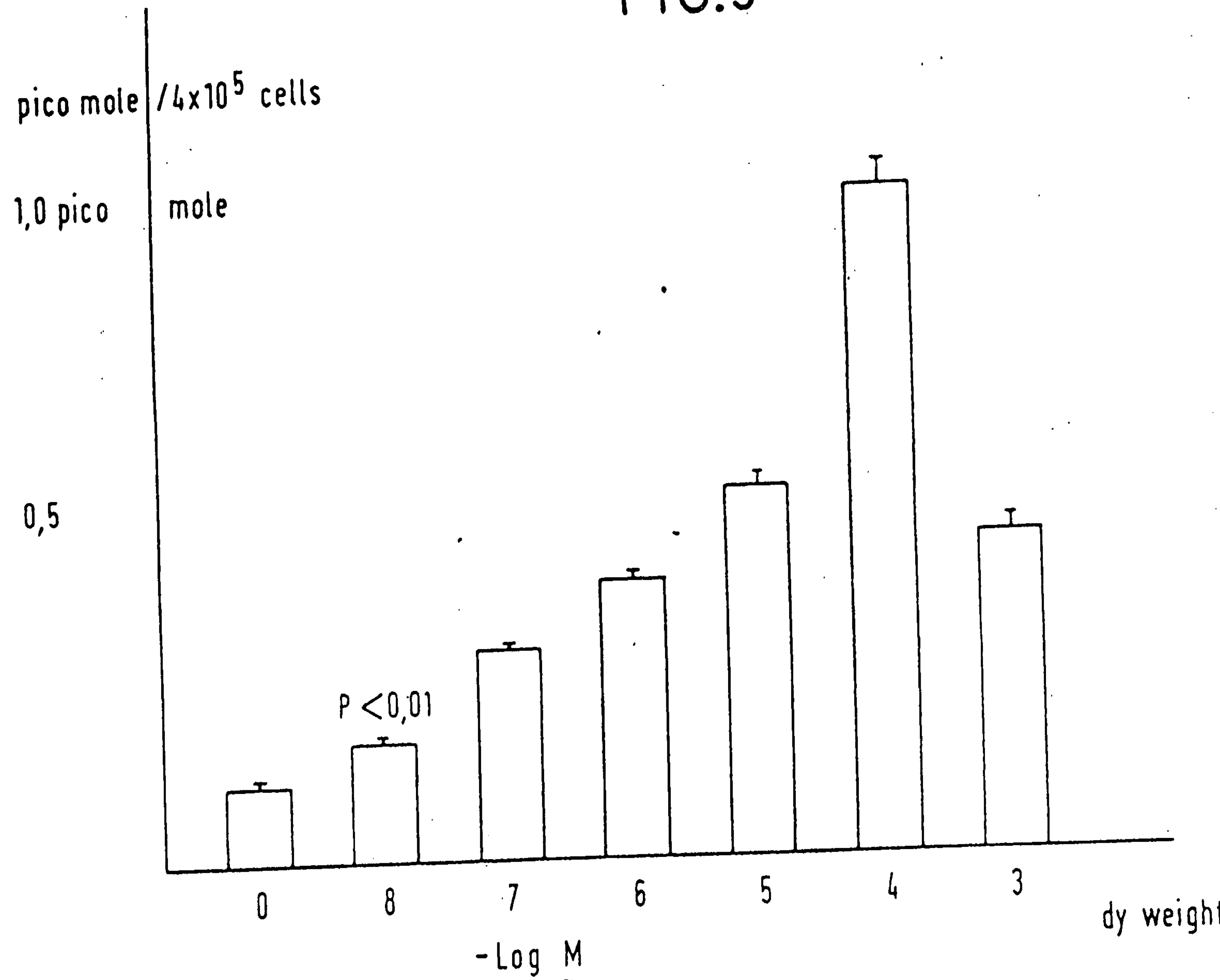

pico mole /4x10^5 cells
1,0 pico mole
0,5
P <0,01
0
8
7
6
5
4
3
dy weight
-Log M

FIG.4

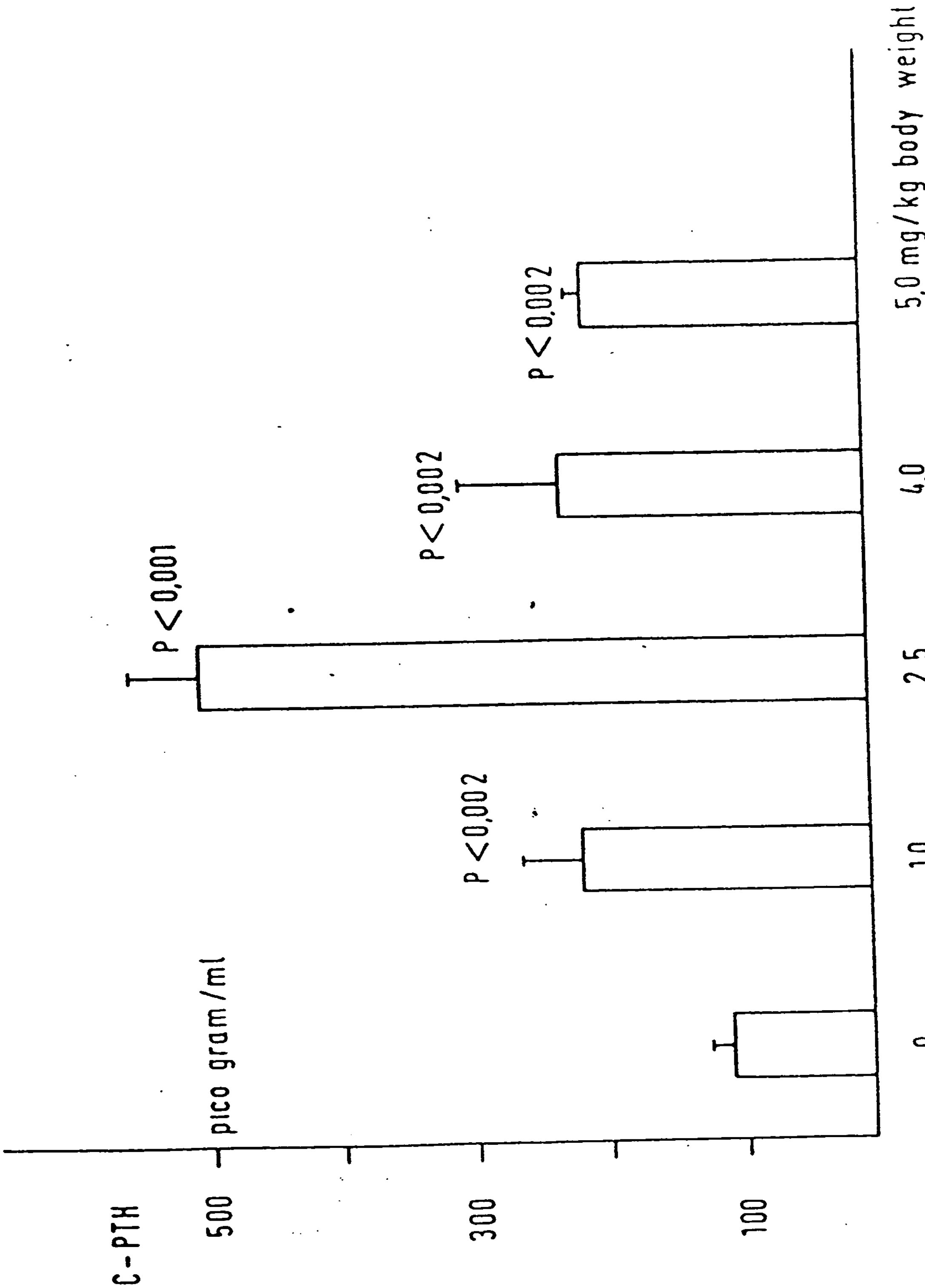
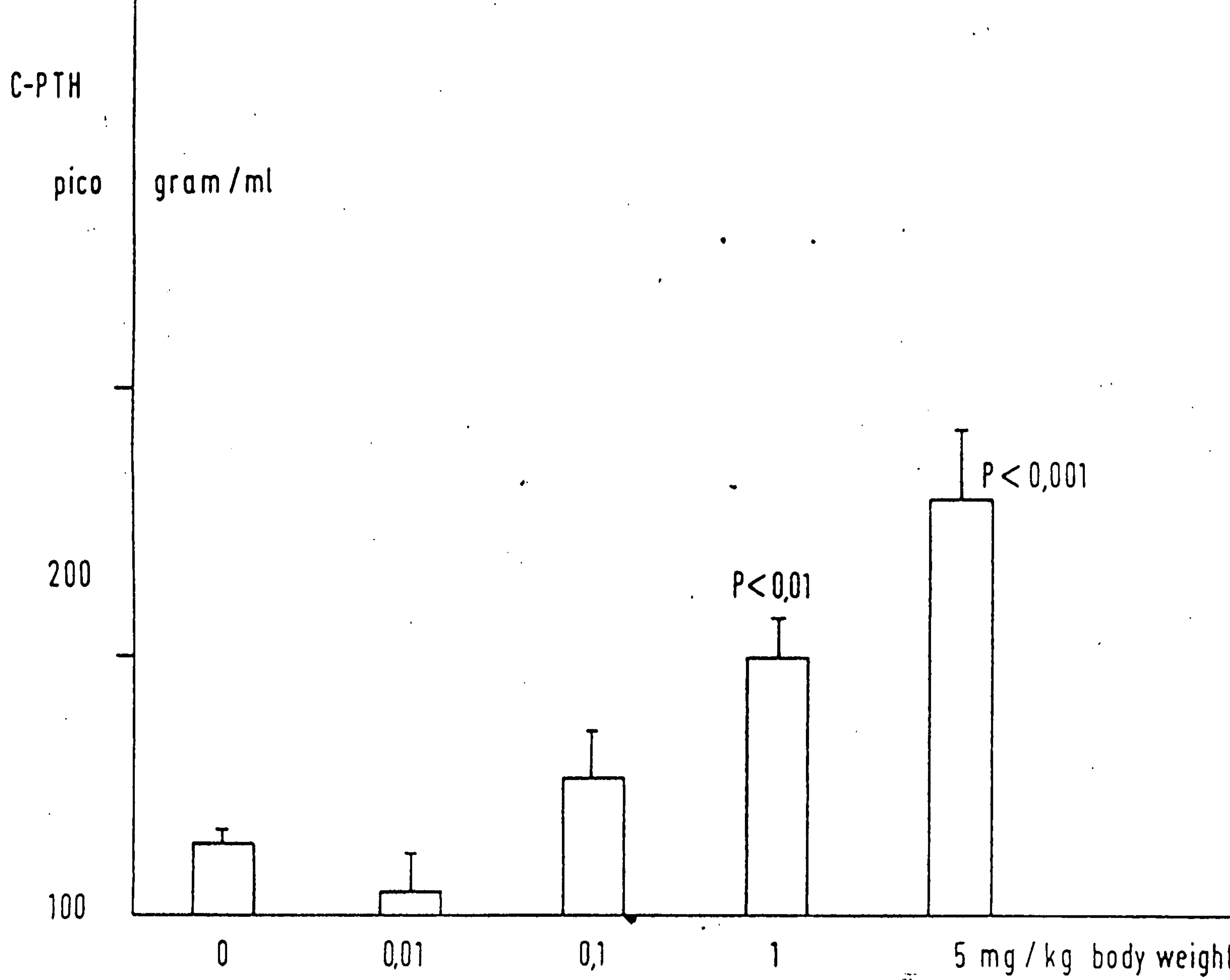

C-PTH
pico gram/ml
500
300
100
P < 0,002
P < 0,001
P < 0,002
P < 0,002
0
1,0
2,5
4,0
5,0 mg/kg body weight

FIG. 5


C-PTH
pico gram / ml
200
100
0
0,01
0,1
1
5 mg / kg body weight
P < 0,01
P < 0,001

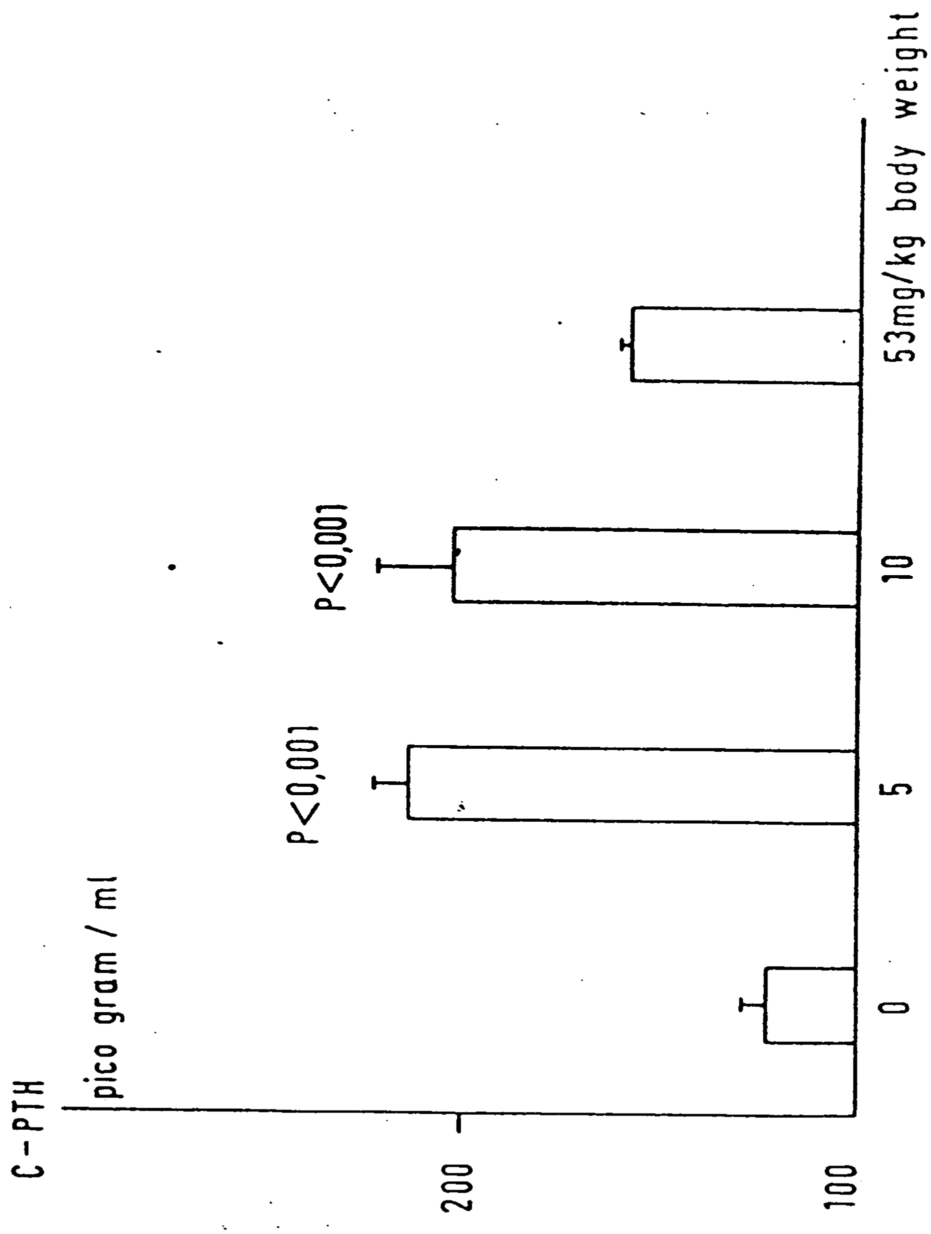

C-PTH
pico gram / ml
200
100
0
5
10
53mg/kg body weight
P<0,001
P<0,001

FIG.6

FIG.7

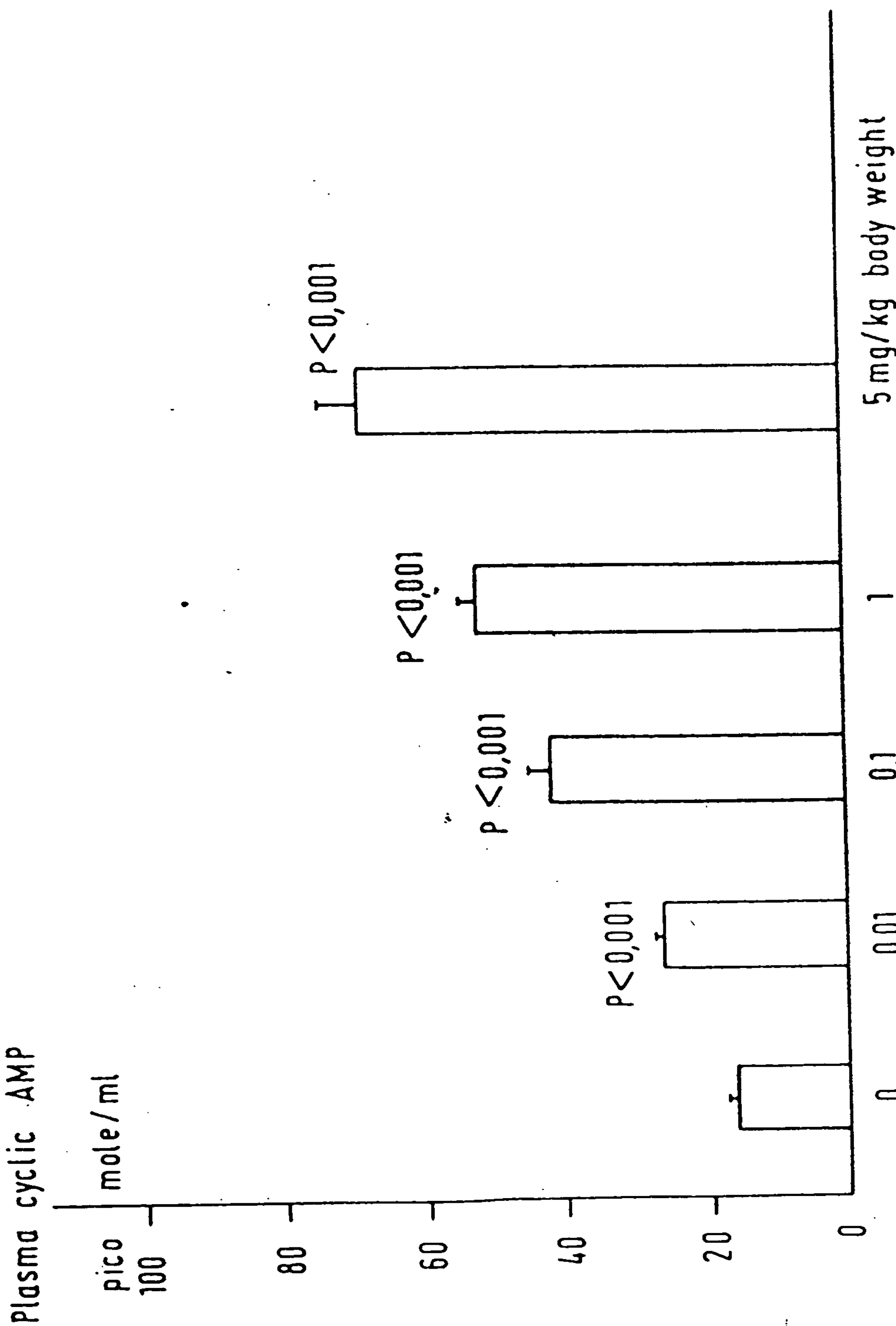
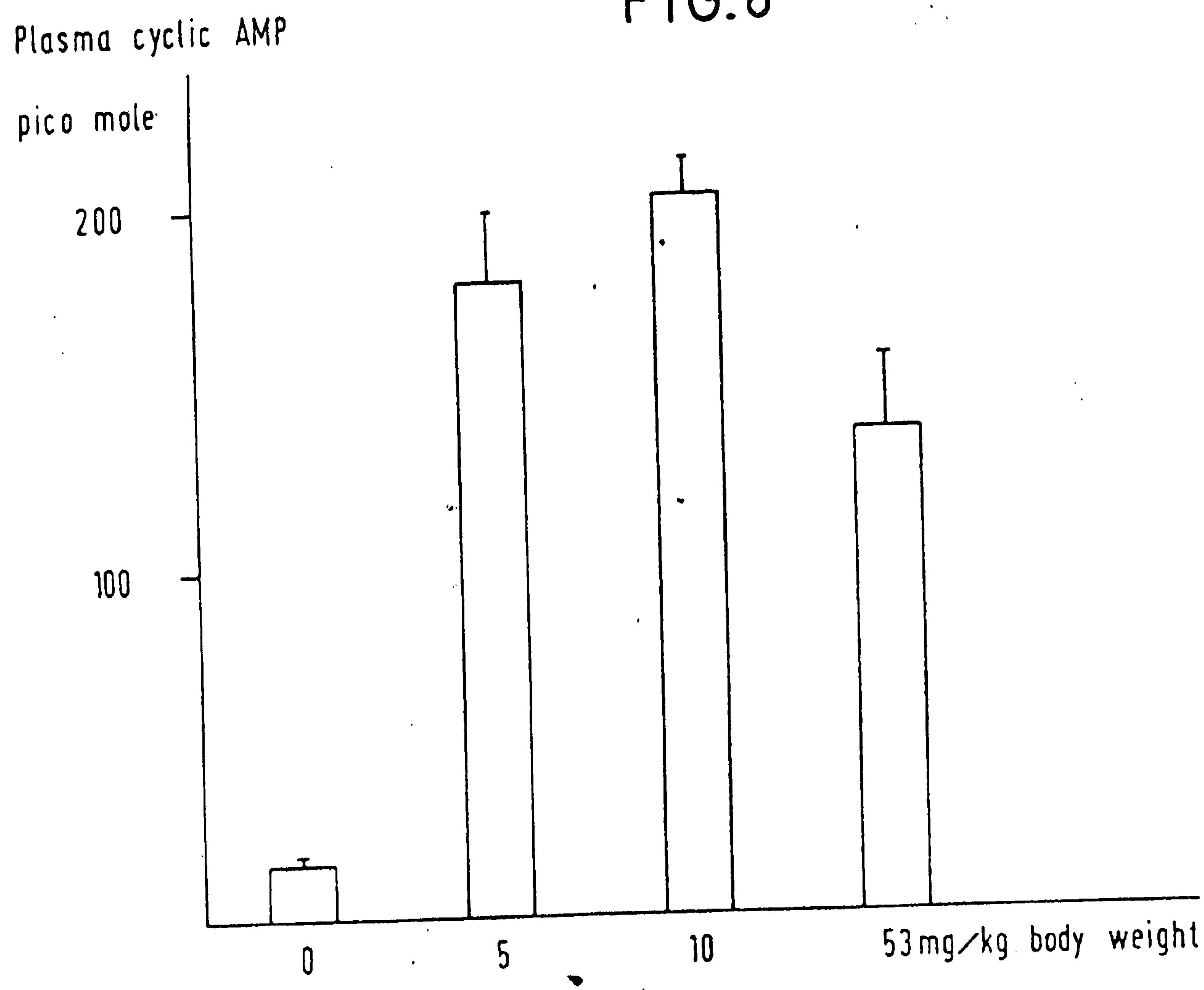

Plasma cyclic AMP
pico mole/ml
100
80
60
40
20
0
P<0,001
P<0,001
P<0,001
P<0,001
0
0,01
0,1
1
5 mg/kg body weight

FIG.8



European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 83103562.1

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
A	GE - A - 2 058 782 (EISAI CO. LTD.) * Claims 1,12,15 * ----	1,7,8	C 07 C 103/60 C 07 C 103/66 C 07 C 102/04 A 61 K 31/16 A 61 K 31/215
			TECHNICAL FIELDS SEARCHED (Int. Cl. 3)
			C 07 C 102/00 C 07 C 103/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	21-06-1983	HOFBAUER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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